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Recent Advances in
GLAUCOMA MANAGEMENT

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RECENT ADVANCES IN GLAUCOMA MANAGEMENT

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PREFACE

Glaucoma is a challenging disease to manage and prevalence estimates in India vary from 2-13%. There have been exciting advances in this field in recent times. We now have a deeper understanding of glaucoma with new drugs, diagnostic modalities and novel therapeutic approaches in our armamentarium. The experts, under the aegis of the ARC AIOS, pool together their expertise, experience and knowledge gained from recent literature to create a comprehensive overview of latest developments in this field. The text is vividly illustrated with videos and clinical pictures to give the reader a virtual "hands on" experience. The content is comprehensive and concise with excellent clarity. We hope it will be useful for the novice and experienced clinician alike.

The field of glaucoma management is constantly evolving and it behoves us as clinicians managing glaucoma to stay updated. We have added references after each section to give a truly enriched learning experience. I sincerely request each one of you to make full use of this book.

I wish to thank all the authors for having taken time out of their busy schedule and contributing to this work. We have decided to roll this out as a ebook to enable wider access during this pandemic. I welcome suggestions to improve this work. You may reach me directly at the Email provided below.

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EDITORIAL

Glaucoma is an umbrella term used for a family of diseases commonly characterised by progressive optic neuropathy with associated visual field deficits. Though it is recognized to have a multifactorial etiology, elevated intraocular pressure (IOP) is one of the primary risk factors, and the only one which may be modified. The main goal of glaucoma management remains control of elevated IOP in an effort to retard disease progression and maintain visual function.

In recent years, there has been a constant effort to maximize the effect of anti-glaucoma medications with minimal associated side effects. While most clinicians still rely on topical medications as first-line therapy, issues with compliance and adherence often limit their effectiveness. Among the challenges are side effects that patients can't tolerate, forgetfulness, dexterity problems that hamper instillation, access to medications, and high costs.

Newer lasers have been added to our armamentarium to reduce IOP in all stages of glaucoma. There is now a recognized role for selective laser trabeculoplasty (SLT) as initial therapy for open-angle glaucoma and ocular hypertension. Novel laser applications (micropulse diode laser trabeculoplasty, titanium sapphire laser trabeculoplasty and excimer laser trabeculotomy) have shown favorable early results. Endoscopic and transscleral cyclophotocoagulation (ECP, TCP) are generally reserved for refractory glaucomas, although some recent studies report its use in patients with good visual acuity.

Trabeculectomy is the mainstay of glaucoma surgery for many decades, and optimizing results of trabeculectomy is an ever evolving science. Understanding surgical techniques and post-operative management is imperative for good outcomes.

Despite the utility of trabeculectomy, it is now recognized that moderate glaucomas may be managed by lesser invasive and safer surgical modalities. The group of minimally invasive glaucoma surgery (MIGS) is a major step in that direction, though the cost effectiveness is still a matter of concern. Though none of the newer procedures gets pressures as low as trabeculectomy, their safety profiles are so appealing that surgeons may want to try them as a first-line treatment.

The review discusses recently introduced paradigms in glaucoma management with an attempt to understand the utility of each modality depending upon the individual patient.

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CONTENTS

WHAT IS NEW
IN
MEDICAL THERAPY OF GLAUCOMA

Dr. Gaurav Gupta, MS
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Medical therapy is the mainstay of treatment in the management of Glaucoma. Traditionally most of the medical therapy for glaucoma is focused on lowering intraocular pressure. Commonly used drugs are prostaglandins, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, etc. Among these prostaglandins are the first line drugs and most commonly used of all. All these drugs are focused on either aqueous formation suppression or increasing outflow from the uveo-scleral pathway.

Newer drugs have come up which focuses on increasing outflow via the conventional pathway. Also, since some patients progress despite IOP lowering. new modalities of medical therapy have focussed on neuroprotection also. Not only drugs but newer drug delivery systems have also come up which focus on decreasing the frequency of drug instillation, increasing the efficacy, and decreasing the ocular surface side effects of existing anti-glaucoma medications.

In this section, we will describe the newer anti-glaucoma drugs and newer drug delivery systems.

NEWER DRUGS:

1. Rho-associated coiled-coil-forming protein kinase (ROCK) inhibitors.

Rho-associated coiled-coil-forming protein kinase (ROCK) inhibitors are serine/ threonine inhibitors that act as selective inhibitors of the actin cytoskeleton contractile tone of smooth muscle in the trabecular meshwork. The only class of anti-glaucoma medications acting upon the cells of trabecular meshwork (TM) and Schlemm's canal (SC), reorganizing the extracellular matrix leading to improvement in aqueous outflow through the trabecular pathway. Its multimodal mechanism also includes a decrease in aqueous secretion and episcleral venous pressure.[1] Some animal studies have shown that ROCK inhibitors may improve optic nerve head supply, increase ganglion cell survival, and reduce scarring, serving in bleb modulation in glaucoma surgery.[2]

Ripasudil (K-115, Kowa Ltd, Nagoya, Japan) is the first Rho kinase inhibitor that has been approved for ocular hypertension (OHT) and open-angle glaucoma (OAG) therapy. 0.4% solution of the drug is to be used as a twice-daily application. Results from the Phase II clinical trial showed that the drug reduced IOP by 3.1 mm Hg from a baseline of 23 mm Hg when used in concentrations of 0.4%. It has a favorable safety profile as well.[3]

Netarsudil is a recently developed IOP-lowering medication that has been approved by US-FDA for OAG and OHT. It is available at 0.02% and has convenient once-daily dosing. Three major trials have evaluated

the efficacy and safety of netarsudil; ROCKET-1 and ROCKET-2 evaluated the efficacy and safety of netarsudil 0.02% in patients with OAG and OHT, and ROCKET-4 compared the efficacy and safety profile of netarsudil once daily vs timolol twice daily. Netarsudil is found to be effective in lowering the IOP up to 22%. Netarsudil once daily was found to be more effective than timolol. Netarsudil was less effective than latanoprost by ~1 mm Hg in patients with unmedicated IOPs in the range of 22–35 mm Hg, while showed similar efficacy when the baseline IOP was ≤26mm Hg.[4-6]

The most commonly reported adverse effect with these drugs is conjunctival hyperemia, which has been reported in 52-57% of cases, but The ROCKET-1 study found that mostly hyperemia was usually reported by the investigator and was unnoticed by patients. A subconjunctival hemorrhage is the second most common adverse effect of netarsudil which is commonly a small, unilateral petechial microhemorrhages in or around the limbus. Cornea verticillata is another prevalent adverse effect of netarsudil. It was present in incidences of 5.4, 25.5, and 24.5% in the ROCKET-1, ROCKET-2, and ROCKET-4 trials, respectively. Other side effects include instillation-site pain, erythema of the eyelid, blurred vision, increased lacrimation.[4-6]

2. Latanoprostene Bunod

It is nitric oxide (NO)-donating prostaglandin analogue approved in the US for the reduction of IOP in patients with OAG or OHT. NO relaxes the TM cells and facilitates the trabecular outflow. NO synthetase is mainly found in the anterior segment, non-pigmented epithelium of ciliary processes, ciliary muscle, TM, SC, and collector channels. These structures efficiently respond to NO and increase outflow in response to NO. NO also regulates ocular blood flow and may promote retinal ganglion cell survival in the eye.[7-9]

It is available in a 0.024% once-daily dosing schedule. Various studies have found it to be effective in IOP lowering. 27% reduction of IOP was observed in glaucoma patients even if IOP is within a normal range.[10] Its IOP lowering effect was found to be more than latanoprost in another study.[11]

Overall, the adverse effect profile of Latanoprostene Bunod was similar to that of prostaglandin analogues. The most common adverse effects are conjunctival hyperemia (17.7%), growth of eyelashes (16.2%), eye irritation (11.5%), and eye pain (10.0%), increase in iris pigmentation (9%).[12]

3. Adenosine Receptor Agonist

Adenosine receptor agonists stimulate the secretion of matrix metalloproteinases (MMPs) in the endothelial cells lining the TM, which causes cell volume shrinkage and remodeling of the extracellular matrix, thereby, resulting in increased conventional aqueous outflow.[13] Trabodenoson (INO 8875) (Inotek Pharmaceuticals, USA) is an adenosine A1 receptor agonist currently in Phase III clinical trial. Can-Fite Biopharma (CF-101) is an adenosine receptor A3 Agonist currently in a Phase II trial stage.[14,15]

4. Bamosiran

Bamosiran (SYL040012) (Sylentis, Spain) is a naked double-stranded small-interfering RNA. It acts through specific gene silencing and causes beta-2 adrenergic receptor blockade, thereby decreasing aqueous production by the ciliary body. It is preferentially taken up by the ciliary body cells, hence unwanted systemic side-effects are avoided.[16]

5. Prostanoid Receptor Agonist

Recently, EP2, EP3 receptors have emerged as new targets of interest for IOP-lowering therapy. These agonists cause relaxation of endothelial cells in the Schlemm's canal, facilitating uveoscleral outflow. They also increase conventional outflow by acting on the trabecular meshwork, decreasing cell contractility and collagen deposition. DE-117 (Santen Pharmaceutical, Japan) and Taprenepag isopropyl (PF-04217329) is EP2 agonist. ONO-9054 (Ono Pharmaceuticals, Japan) has dual action of being an EP3 agonist and FP receptor agonist.[17,18]

CONCLUSION:

Various newer drugs for IOP lowering have come up which give new hopes in the treatment of Glaucoma. Long-term studies and randomized control trials are needed to establish the efficacy and superiority of these newer drugs over existing drugs. Combination therapies are being tried to increase efficacy, decrease the frequency and increase patient compliance.

NEWER DRUG DELIVERY SYSTEMS

Conventional topical drug therapy is usually effective in the treatment of glaucoma in most cases but is still associated with practical problems like issues of compliance, difficulty in sustained 24 hours IOP control, and ocular surface side-effects. In an effort to circumvent these challenges, several new anti-glaucoma therapies with sustained effects have emerged. Methods for sustained delivery of prostaglandin analogs are being intensely investigated and many are in clinical trials.

INTRACAMERAL SUSTAINED RELEASE IMPLANTS

Bimatoprost Intracameral Implant

Durysta™ (Allergan plc, Dublin, Ireland) has received FDA approval for humans with OAG and OHT in March 2020. It is a 400 X 1100 micron rod-shaped implant, supplied pre-loaded for intracameral injection in a 28G customized applicator. The bioerodible implant contains 10µg of bimatoprost which is released in a steady sustained fashion for 3 to 4 months. This implant is well tolerated and visible only on gonioscopy in inferior angle.[19,20] Bimatoprost-associated effects included dose-related mild to moderate conjunctival hyperemia and miosis, both of which tended to diminish as the implant degraded. The conjunctival hyperemia is due to vasodilation and not inflammation.

Bimatoprost SR intracameral implants are believed to lower IOP by increasing aqueous humor outflow both via the trabecular meshwork and uveoscleral routes. It also causes a sustained decrease in episcleral venous pressure. Bimatoprost SR decreases IOP more than topical therapy. The additional IOP reduction with Bimatoprost SR versus topical therapy may also be related to the implant achieving a 4,400-fold higher drug concentration in the iris-ciliary body than topical administration. It may cause long-lived anatomic or physiological remodeling of the outflow pathway that persists after the drug is no longer present. This durable remodeling may explain why in phase I/II and III human clinical trials, 28%-36% of patients still had not required topical IOP-lowering rescue medication or implant retreatment 2 years after a single administration of an implant, even though the implant was depleted of drug long ago.[19-21]

Travaprost Intracameral implant

iDose Travaprost

The iDose implant by Glaukos (San Clemente, CA, USA) is an indwelling depot device designed to provide sustained-release of travoprost to the anterior segment for periods of 6 months or longer. It is implanted by ab interno procedure placed in tandem with routine phacoemulsification. The iDose is a 1.8 mm X 0.5 mm titanium implant designed to be anchored within the trabecular meshwork. The iDose implant is currently recruiting patients for Phase III clinical trials, and interim results have been reported from a double-masked Phase II trial in human patients. In the phase II trial, those patients receiving iDose implants experienced 32%-33% IOP reduction at 1 year.[22,23]

ENV515

ENV515 by Envisia Therapeutics (Morrisville, NC, USA) is a biodegradable intracameral travoprost implant. In the preclinical studies, the implant was highly effective at lowering IOP, well-tolerated, and tended to stably rest in the inferior angle. In human clinical trials, a single ENV515 implant lowered IOP 25% over 11 months in 5 human glaucoma patients with no loss of efficacy over this period.[24,25]

Bimatoprost Topical Ring Insert

Allergan (Irvine, CA, USA) has developed a preservative-free flexible ring ranging from 24-29 mm in diameter which is designed to be placed in the fornix and to circumferentially contact the conjunctival surface. It contains 13 mg of bimatoprost. The drug diffuses from the silicone matrix directly into the tear film. In a 6-month Phase II clinical study of patients with OAG or OHT, the mean reduction in IOP compared was similar between eyes receiving the bimatoprost loaded ring and a placebo non-drug-loaded device combined with 0.5% timolol eye drops BD. Mucoid discharge is the most common side-effect. Other less common are conjunctival hyperemia, punctate keratitis, and ocular pruritus.[26]

Travoprost Punctal Plugs

OTX-TP intracanalicular travoprost implant by Ocular Therapeutix (Bedford, MA, USA) are also commonly known as 'Travoprost Punctal plugs'. These are sustained ocular drug delivery implants, which are placed into the inferior nasolacrimal canaliculus that releases drug to the ocular surface via the inferior punctum. These are proven to release travoprost for 2-3 months. Unfortunately, the device was not found to be

superior to timolol in a Phase IIB human clinical trial and also did not achieve its primary endpoint in a Phase III human clinical trial.[27,28]

Contact Lens-Based Drug Delivery

Silicone hydrogel soft contact lenses are loaded with the nanoparticle. The drug diffuses from the lens into the tear film, increasing the bioavailability potential by 50%, as against topical formulations with only 1%–5%bioavailability. Silicone hydrogel soft contact lenses containing timolol have been found to elute the drug for more than a month in animal models.[29]

Nanoparticle-Based Drug Formulations

Nanoparticle on a scale 10–1000 nm serves as vehicles for drug delivery. They are bioinert, biodegradable, and mucoadhesive polymers that aid corneal penetration of the drug. Commercially available ophthalmic nanotechnology is Timoptic-XE, a pH-sensitive hydrogel formulation of timolol that turns from a solution to a gel when it comes in contact with cations in the tear film, enhancing the delivery of the drug to the ocular surface.[30] Nanoparticle technology has also been incorporated in contact lenses for sustained drug delivery. They have also been tried to be used as an adjunct to glaucoma drainage devices to decrease fibrosis.

CONCLUSION:

Many novel drug delivery approaches are in development and many have the aim of improving the effectiveness of therapy, patient adherence, and the elimination of issues associated with the traditional self-administered drops. However, long-term trials are needed to establish the safety and efficacy of these newer modalities. Also, the cost-benefit ratio of these new devices can be an important factor in consideration.

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Notes:

SELECTIVE LASER TRABECULOPLASTY

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Trabeculoplasty was introduced in the early 1970s. Though Argon laser trabeculoplasty(ALT) was first described in 1974 by Worthen and Wickham[1], it was in 1979 after being modified by Wise and Witter that the technique became popular[2]. Later the Glaucoma Laser Trial proved the technique to be as effective as timolol in the treatment of open angle glaucoma[3]. However, the structural damage caused to the trabecular meshwork was considered to affect the success of repeat ALT.

In 1995 Latina and Park introduced Selective laser trabeculoplasty (SLT)[4], which selectively targets only the pigmented cells of trabecular meshwork using 532-nm, frequency doubled, Q-switched Nd: YAG SLT laser (Fig1 SLT-Yag Combo unit).

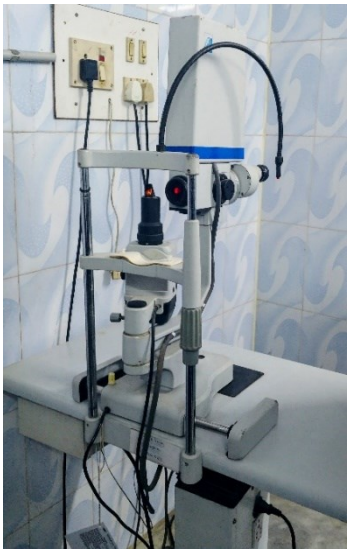

Figure 1: Q switched Nd : YAG SLT device

Mechanism of action:

Biomechanical Theory

The proposed mechanism of action is to increased aqueous outflow. Various studies have shown that the laser, both ALT and SLT stimulate increased cellular activity by up- regulation of interleukin 1 and tumor necrosis factor. This pushes more macrophages into the trabecular meshwork and activates metalloproteinase expression and thus remodelling of extracelluar matrix and increasing the aqueous outflow[5,6].

The **mechanical theory** where the electromagnetic energy is converted into thermal energy which causes contraction of collagen and thus opening up the Schelmn's canal[7] is considered as a possible mechanism for the working of ALT besides the **Cellular theory** which hypothecated increased aqueous filtration by new trabecular cells produced by increased cell division due to the laser[8].

In contrast, SLT causes lesser structural damage to the trabecular meshwork. This is because SLT selectively photolyses pigmented TM cells without causing photocoagulation and collateral damage to non-pigmented cells as its pulse duration is shorter (3 nsec) than the thermal relaxation time of melanin (1msec)[9].

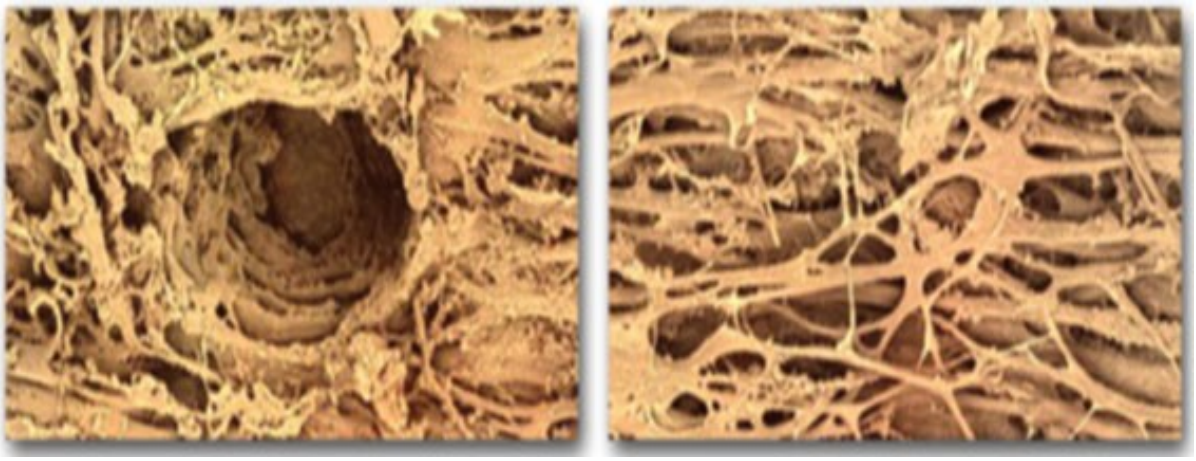

Figure 2: Tissue damage caused by ALT as compared to SLT

Indications[10]:

1. Open angle glaucoma like primary open angle glaucoma, ocular hypertension, pigmentary glaucoma, pseudo- exfoliation glaucoma and psuedophakic glaucoma.
2. Primary therapy when there is poor drug compliance, pregnancy/lactation
3. Supplement to medical therapy and to postpone surgery
4. To lower IOP after surgery/trabeculectomy
5. After failed previous ALT

Contraindications[10]:

1. Angle closure glaucoma when Trabecular meshwork cannot be well visualised
2. Inflammatory glaucoma - uveitic, neovascular and post traumatic glaucoma are relative contraindications
3. Congenital and Developmental glaucoma
4. Aphakia with vitreous in anterior chamber
5. Media haze

Procedure[11, 12]:

A complete glaucoma evaluation including gonioscopy ensuring visibility of angle structures and landmarks such as trabecular meshwork, grade of trabecular pigmentation and the extent/presence of gonio synechiae should be performed. Corneal wedge would help in discerning the structures especially in pigmentary and pseudoexfoliation glaucoma where the Sampolesi's line could easily be mistaken for posterior trabecular meshwork.

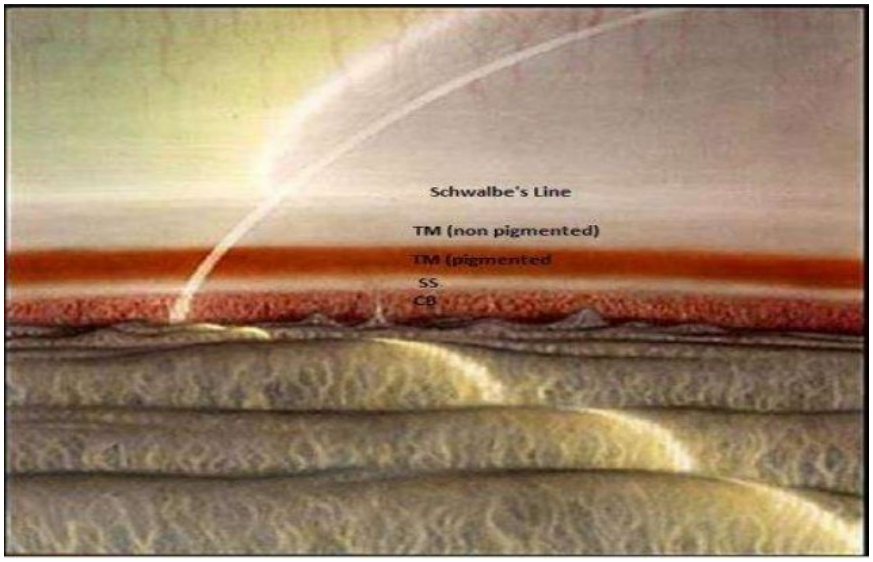

Figure 3a: Identifying angle structures using corneal wedge

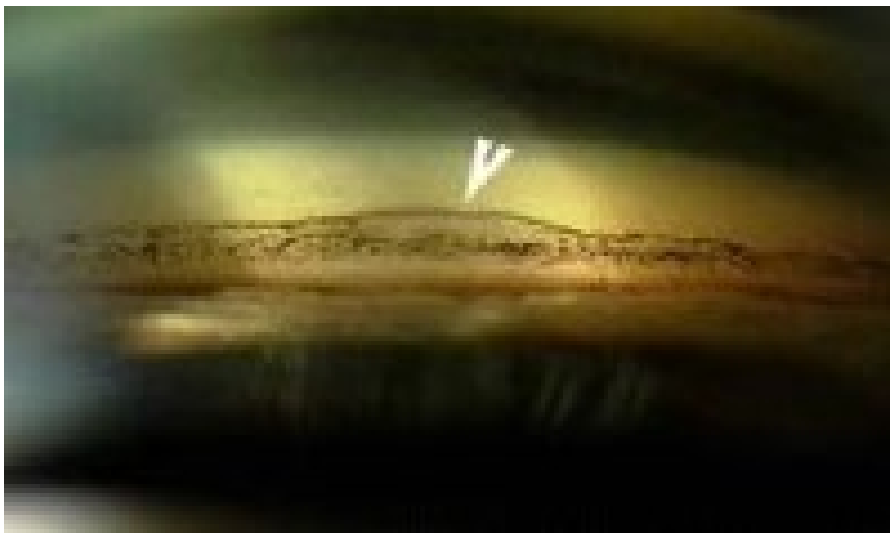

Figure 3b:
Sampolesi's line in eyes with pseudoexfoliation mimicking posterior trabecular meshwork

- Topical anaesthesia is applied.
- Latina trabeculoplasty lens or Volk Rapid SLT lens is used.

Figure 4a: Latina SLT lens

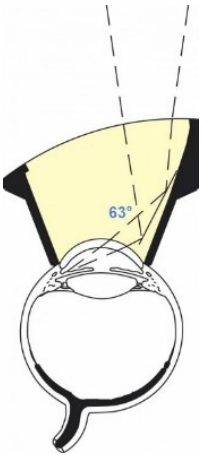

Figure 4b: The large 63^0 angled mirror aids in the visualisation of angle structures

Figure 5: Volk rapid SLT lens

- The laser settings are fixed except for the power. Spot size is 400-microns and pulse duration is 0.3 ns. The large spot size covers the entire width of the posterior trabecular meshwork.
- The initial power is set at 0.8 mJ and titrated to achieve small cavitation bubbles, "champagne bubble" appearance. These bubbles may indicate over treatment. Once bubbles are noted the surgeon scales down the energy to continue with SLT. SLT treatment energy may vary depending on TM pigmentation.
- In an eye with normal TM pigmentation it is the practioner's preference to do 360 degrees SLT in single sitting but in eyes with dense TM pigmentation an initial 180 degree treatment is done to assess the response before treating rest of the angle.
- About 50 non- overlapping spots over 180 degrees or 100 spots over 360 degrees is applied.

- Post laser anti- glaucoma medications are continued for a few weeks. The role of non steroidal anti- inflammatory medications and steroids has been widely studied and it is the treating practioner's preference to avoid usage of these.
- Intraocular pressure is checked after an hour, 1 week and after 1 month.It usually takes about 4-6 weeks for the laser to take effect.

Adverse Effects:

- Intraocular pressure spike: Most studies show intraocular pressure spike in the first few hours to days after laser[12] treatment which usually responds to topical intraocular pressure reducing agents. Very rarely the pressure elevation is prolonged especially in heavily pigmented trabecular meshwork[13].
- Inflammation: Mild to moderate anterior chamber reaction has been reported which usually is self- limiting[12].
- Few cases of pain, corneal haze possibly due to herpes virus[14] reactivation and hyphaema[15] have also been reported.

Success Rates:

- SLT showed similar efficacy rates compared to ALT at short and long term as confirmed by several studies[16, 17, 18].
- SLT has been found to be non- inferior to anti glaucoma medications when offered as initial glaucoma treatment[19, 20].
- A multicenter randomized controlled trial comparing SLT as primary treatment for open angle glaucoma and ocular hypertension showed better intraocular pressure reduction and cost effectiveness with SLT[21, 22].
- Success rates of SLT were comparable for OAG and pseudo exfoliation glaucoma[23].
- The amount of pigmentation of the trabecular meshwork did not influence the success rates of SLT[23].
- Higher pre- laser intraocular pressure was found to associated with better IOP lowering with SLT[24].
- Success rates of repeat SLT after failed ALT was found to be significantly better than repeat ALT[25].
- There was no difference in the efficacy of SLT between phakic and pseudo phakic eyes[26].

LiGHT Trial (Laser in Glaucoma and ocular Hypertension)[27]

It is a multicentre randomised control trial where SLT and eye drops were compared as first line treatment options for open angle glaucoma and ocular hypertension. 718 patients were randomised with 356 being treated with SLT and 362 with eye drops. 91 % of patients completed the trial of 3 years. Questionnaire for assessing quality of life by EQ- 5D and success rate in term of intraocular pressure reduction and number of anti- glaucoma medications used or need for trabeculoplasty was assessed.

It was found that the EQ- 5D was not statistically different between the two groups. The groups also had similar visual acuity and visual field loss as measured by mean deviation at the end of trial. 95% of SLT eyes were at target iop with or without medications compared to 93% in the eye drops group. None of the SLT group patients required glaucoma surgery compared to 11 in the eye drops group. Also SLT was found to be more cost effective as about 74 % of SLT eyes did not require anti- glaucoma medication at the end of trial. Thus the trial supports SLT as a viable alternative to anti- glaucoma eye drops as the first line treatment in patients with open angle glaucoma and ocular hypertensives.

Pattern laser trabeculoplasty:

This uses computer guided laser technology to apply a sequence of laser spots to the trabecular meshwork. The aiming beam rotates automatically, thus reducing time of treatment and also ensures correct placement of the spots.

Micropulse laser trabeculoplasty:

Here subthreshold pulsed laser, i.e.; 15% of the duty cycle is used to treat the trabecular meshwork. It is considered to be less scarring and avoids cellular destruction.

Difference in spots between the various types trabeculoplasty

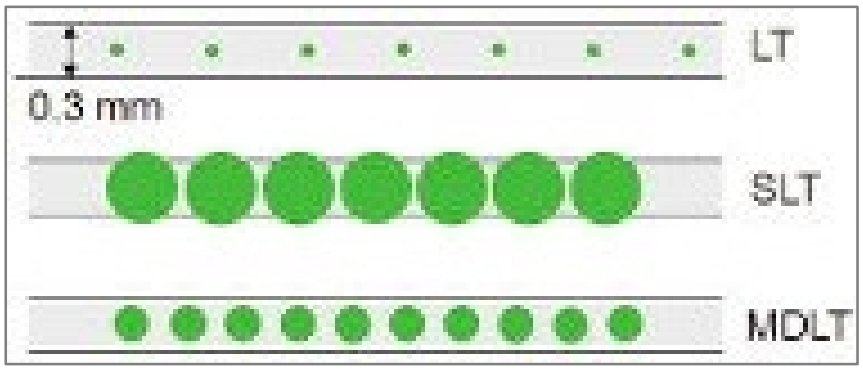

Fig 6: Difference in spot size with ALT SLT and MLT

Nano SLT:

It is a recent version of the SLT in that there is higher pulse to pulse stability. Here the pulse duration of the laser is just 1 nano second making the procedure faster and safer.

Suprathreshold SLT:

As the name suggests in this method the energy is increased by 0.1m J beyond the optimal champagne bubble end point in that of SLT to knock out the pigment granules of trabecular meshwork.

Table 1: Comparison between MLT SLT and ALT

	MLT	SLT	ALT
Wavelength	532 nm, 577 nm	532 nm	488/514 nm, 532 nm
Mechanism	Thermally effects - not destroys - pigmented TM cells	Selective destruction of pigmented TM cells without thermal or collateral damage	Shrinkage of TM with adjacent stretching
Repeatable	Yes	Yes	No
Treatment Endpoint	No visible tissue reaction	Small bubbles	Blanching (mild) to bubbles (intense)
Post op Inflammation	None	Yes	Yes
Spot Size	300 µm Smaller spot to access narrow angles	400 um	50 um

To conclude SLT is a useful addition and alternative to topical glaucoma medication in mild and moderate open angle glaucoma cases especially considering the relatively fewer complication rates and report cost-efficacy benefit in SLT treated patients. Few of the concerns and practical problems include its long term efficacy and paucity of Indian data besides acceptance/availability of this technology across the country.

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Notes:

MICROPULSE TRANS-SCLERAL DIODE LASER CYCLO-PHOTOCOAGULATION (MP TSCPC)

Dr. Murali Ariga, MS, DNB, FAICO
Dr. Pratheeba Nivean, MS

Glaucoma is a leading cause of irreversible blindness worldwide. Glaucoma is defined as an optic neuropathy characterised by progressive degeneration of the retinal ganglion cell layer, with typical optic disc and retinal nerve fibre layer (RNFL) changes and irreversible visual field loss.[1] Treatment aims at lowering intraocular pressure (IOP), either by reducing aqueous humour production or by increasing its outflow through the trabecular or uveoscleral routes or both. Treatment options include topical medications, laser, trabeculectomy, minimally invasive glaucoma surgery, glaucoma drainage implants and cycloablative procedures.[2] Treatment would depend on various factors like the severity of the disease, response to treatment and the clinical judgement of the treating physician.

Cyclo-ablative procedures such as Trans scleral Diode laser cyclophotocoagulation (TSCPC) have generally been reserved for refractory glaucomas and there are reports about the risk of developing serious complications with this procedure, such as persistent ocular inflammation, vision loss, hypotony, phthisis bulbi and even rarely sympathetic ophthalmia.[3-5] This led to the development of a new treatment option, the micro-pulse diode trans scleral cyclophotocoagulation (MP-TSCPC) which is now being used to lower IOP by delivering repetitive short pulses of 810 nm infrared diode laser radiation. [6-10] This allows energy to reach the coagulative threshold in the targeted pigmented tissues with minimal collateral disruption of the nonpigmented epithelium, the ciliary body stroma and adjacent tissue.

Mechanism of action

Transscleral cyclophotocoagulation (TSCPC) is a cyclodestructive procedure designed to target the melanin in the pigmented ciliary body epithelium, thereby decreasing the rate of aqueous humour production. TSCPC conventionally uses the continuous wave diode laser and has been reserved for the treatment of refractory glaucoma or palliation of painful eyes that have poor visual prognosis as the complications are more with this procedure. It is to be avoided in eyes with good visual function.

The more recently introduced Micropulse Transcleral cyclophotocoagulation (MPTSCPC) (Iridex cyclo G 6 laser) gives repetitive short pulses of 810 nm infrared diode [11-12] laser radiation.

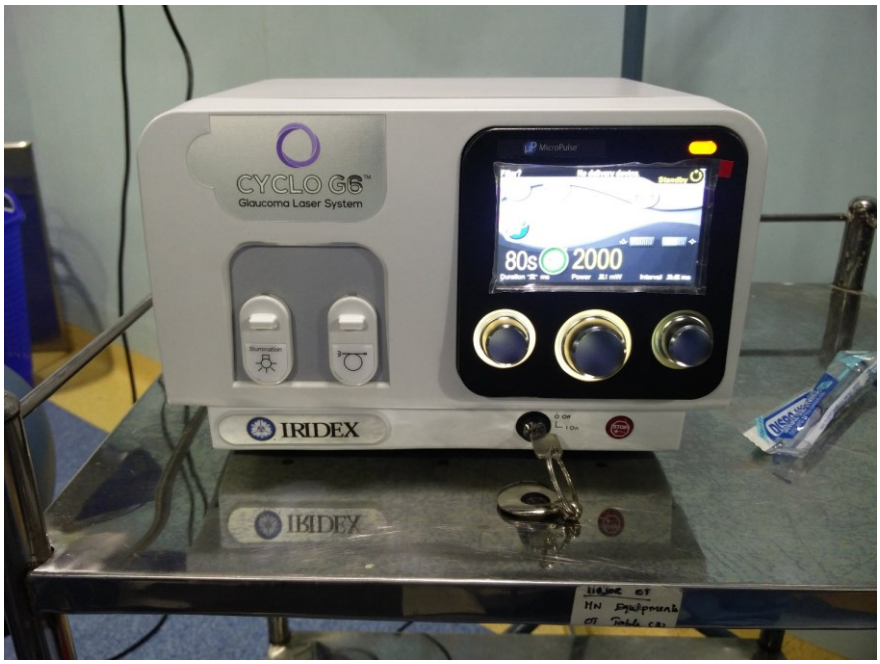

Figure: 1

With its "on" and "off" cycling mode, it allows energy to reach the coagulative threshold in the targeted pigmented tissues with minimal collateral disruption of the nonpigmented epithelium, the ciliary body stroma and adjacent tissue. No major anterior segment anatomic modifications on either ultrasound biomicroscopy or anterior segment optic coherence tomography have been demonstrated following the MP-TSCPC procedure.[11] This is in comparison to the traditionally used continuous-wave TSCPC, in which thermal tissue damage has been confirmed histologically.

Technique

The procedure should be done under retrobulbar or peribulbar anaesthesia with vitals monitoring (SpO2 and NIBP) as per guidelines.

The MP3 probe

Figure: 2

is used with the Iridex Cyclo G6 (IRIDEX Laser Systems), with a standardized preset power of 2000mW and a duty cycle (proportion of each cycle during which the laser is on) of 31.33% (micro pulse "on" 0.5ms, micro pulse "off" 1.1ms) for all patients. The tip is specially designed in a way to fit and adhere to the ocular globe 3mm posterior to the limbus.

The laser probe's fiber-optic tip should be applied with steady pressure in a continuous sweeping motion over 360 degrees for 160 (80 seconds superiorly and 80s inferiorly) seconds on all patients

Figure: 3

A lubricant eye gel (HPMC) should be used for lubriaction before placing the probe on the eye.

During the "on" cycle, the pulses of light emitted near the infrared region at 810 nm are strongly absorbed by melanin in the pigmented ciliary epithelium. The "on" cycle allows the build-up of thermal energy and subsequent photocoagulative thermal damage in the ciliary body. During the "off" cycle, the adjacent non-ciliary structures are allowed to cool, protecting them from thermal damage. This approach reduces the destruction of surrounding tissues, and potentially results in fewer ocular complications without compromising the IOP-lowering .[12]

Complications

The rate of complications with MPTSCPC is reported to be minimal in comparison with traditional TSCPC. This has made it possible to use this procedure successfully even in moderate/refractory glaucomas in eyes with fair to good vision potential. Robert Noecker et al studied the benefits of micropulse TSCPC for early-stage glaucoma treatment and have reported that Micropulse technology, unlike Continuous Wave laser application, does not induce fatal architectural damage to the cellular structure. It can be repeated and is proving to be an effective option to fill the gaps between topical medical therapy, MIGS and traditional glaucoma-filtering surgery as this procedure stops the inflow and also increase the outflow by increasing the porosity in trabecular meshwork.

The common complications include acute inflammation, hyperemia, discomfort, pain, visual loss and corneal edema. Furthermore, William et al found that non-white races were more prone to develop more inflammation and suggested shorter treatment time for them. [12] Radhakrishnan et al. reported higher odds of persistent mydriasis in the Asian race. [13]

A mild but significant decrease in Corrected distance visual acuity (CDVA) in the early follow-up associated with a transient postoperative inflammation has been reported by Zaroor Karen et al. [14] Major complications including phthisis or hypotony were not commonly reported.

Various studies

The initial studies on MPTSCPC were on refractory glaucomas and eyes with poor vision but later on due to its efficacy and fewer side effects this procedure has been tried for even mild to moderate glaucomas in eyes with vision potential. For the purpose of easy understanding we have elaborated a latest single study on the effect of micropulse laser in moderate to advanced glaucoma, early to moderate glaucoma, a comparative study between the standard diode laser photocoagulation and our results. We also have attached the results obtained with micropulse laser published by various authors. (Table: 1) [14]

Zarour karen et al [15] in his perspective, consecutive case series, evaluated the intermediate-term efficacy and safety of a standardized fixed MP-TSCPC protocol in the treatment of medically uncontrolled glaucoma, irrespective of visual acuity and previous surgical therapy. The MP3 handpiece was used with the Iridex Cyclo G6 (IRIDEX Laser Systems), preset power of 2000 mW and a duty cycle (proportion of each cycle during which the laser is on) of 31.33% (micropulse "on" 0.5 ms, micropulse "off" 1.1 ms) for all patients who had moderate and advanced glaucoma.

The percentage of eyes that successfully achieved a decrease of at least 20% of their baseline IOP decreased progressively from 86.7% at 1 month to 67.1% at 6 months and 56.7% in 1 year. Six eyes (8.0%) needed a retreatment session with MP-TSCPC in 15 month study period.

Robert Noeckar etal [16] studied the effect of MicroPulse P3 glaucoma device (IRIDEX IQ810 Laser Systems) in 95 eyes and his settings were 2–2.5 watts with a duration of 90 seconds per hemisphere at a 31.3% duty cycle. In cases requiring re-treatment, the same treatment parameters were used with an increase in power up to 3 watts. He has repeated the procedure based on the need of IOP control over a period of time. The mean preoperative IOP was 25.1 ± 5.3 mm Hg, and the mean postoperative IOP at 12 months was 17.5 ± 5.1 mm Hg ($P = 0.004$) which was very significant and there was a significant drop in need for topical use as well.

There are few comparative studies between the standard CPC and the micropulse laser CPC. Aquino et al[15] found a similar drop in IOP post treatment between the two groups. After 18 months, 52% of patients treated with MP-TSCPC and 30% of patients treated with CW-TSCPC were successful in retaining an IOP of 6-21 mmHg with at least 30% reduction from their pre- operative IOP level. The number of glaucoma medications was reduced from 2 to 1 at 18 months, with no statistical difference between the two groups. There was no significant difference in timing required for retreatment. However the authors reported more complications in the conventional transscleral cyclo-photocoagulation group.

Our prospective study to analyse the outcomes of micropulse TSCPC in Indian eyes was published recently[16]. 55 eyes underwent micropulse diode laser cyclo-photocoagulation using a standard protocol. IOP was 30.38 ± 10.70 mm Hg at baseline. At 1 week, 1 month and 3 months, it was 15.72 ± 6.85, 16.98 ±8.72 and 17.60 ± 8.40 respectively ($p < 0.001$ for all). Use of glaucoma medications was seen to reduce from 2.94 ± 0.98 at baseline to 2.01± 1.16. ($p<0.001$) When analysing outcomes based on type of glaucoma (Table 2), there was no significant difference between groups in surgical success at 1 week and 1 month ($p>0.05$). At 3 months, success was significantly less in the POAG group ($p=0.02$) compared to other groups.

Limitation with studies

Most of the studies had small sample size and relatively short follow up. There is only one comparative study between the conventional CPC and the micro pulse diode CPC. There is no standard protocol being followed in all the studies. Inclusion criteria was different so it is difficult to compare and relate one study

to the other. Needless to say, glaucoma is a progressive disease and one needs long term follow-up to know outcomes of newer treatment modalities.

Conclusion

Micropulse laser photocoagulation can be offered to patients with mild and moderate glaucoma besides refractory glaucomas. It can be offered as a substitute or supplement to topical therapy particularly in patients intolerant to topical medication. However, it should be clearly explained that this procedure is not a permanent cure for uncontrolled glaucoma. The effect of therapy may gradually decline with time and the laser may have to be repeated. There is also some concern about visual loss experienced by few patients after MP TSCPC. This has to be investigated further in longer term studies and patients undergoing this procedure must be counselled regarding the pros and cons of such newer laser procedures. Glaucoma patients also have to be counselled that they require life-long monitoring and follow up.

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Notes:

OPTIMIZING THE OUTCOME OF YOUR TRABECULECTOMY: THE GOLD STANDARD

Prof. Tanuj Dada, MD
Dr. Karthikeyan Mahalingam, MD
Prof. Ramanjit Sihota, MD, FRCS, FRCOphth

Introduction

Intra-ocular pressure (IOP) remains the most important modifiable risk factor to prevent progression of glaucoma. In eyes with uncontrolled intraocular pressure with maximum tolerated medical therapy, surgical intervention is imperative. The filtration procedure that has stood the test of time is Trabeculectomy. Originally described by Cairns,[1] it involves the creation of an ostium in the sclera, guarded by a partial thickness scleral flap; which directs the aqueous from the anterior chamber, into the subconjunctival space. *Trabeculectomy is a high yield, high risk and high maintenance surgery* and we can do some modifications aimed at increasing its safety and improving long-term efficacy.

How does it work?

Trabeculectomy is a guarded filtering surgery wherein the fistula is covered by a partial thickness scleral flap to decrease risk of hypotony and associated complications initially described with full thickness filtering surgeries. [2–4]

External filtration around the scleral flap into the sub-conjunctival space has been found to be the principal mechanism of aqueous drainage after trabeculectomy. *The amount of filtration through the scleral flap depends on the thickness of the flap and the tightness of its closure* and these can be modulated to achieve optimal outcomes. Other mechanisms that have been proposed include-

- Aqueous flow into the cut ends of the Schlemm's canal. (rare)
- Drainage into the cyclodialysis cleft. (in cases where at least a part of the fistula is posterior to the scleral spur)
- Drainage through the aqueous channels in the sclera.[5,6]

The Filtering bleb

This external filtration into the sub-tenon's or the sub-conjunctival space leads to elevation of a part of the conjunctiva, known as the bleb. The bleb morphology in terms of elevation, vascularity and extent can be good indicators of its functionality. Blebs associated with good control of intra-ocular pressure are generally relatively avascular, with numerous microcysts in the epithelium. These blebs may be low and diffuse or elevated and circumscribed. Histologically, well-functioning blebs have loosely arranged collagen in the sub-epithelial tissue, as opposed to failed blebs with densely packed collagen. Fibrosis of the bleb leads to failure of trabeculectomy.

Key Surgical caveats:

- An infection in the conjunctiva or adnexa should be ruled out and mobility of the conjunctiva should be evaluated by elevating and lowering the upper eye lid on the slit lamp to assess for scarring which is the main risk factor for failure.
- Always operate on a "quiet" eye and give a 2-4 week course of topical steroids (flurometholone) to decrease conjunctival inflammation caused by topical glaucoma medications. Keep a check on IOP spikes due to steroid use.
- Preoperatively the IOP should be lowered by intravenous mannitol just before surgery after appropriate medical clearance for systemic diseases.
- A traction suture is passed either under the superior rectus or through the superior cornea. Superior rectus traction suture can trigger fibroblast proliferation as the muscle sheath is injured and has also been associated with globe perforation and post operative ptosis. Use of a corneal traction suture or a special speculum which does not require any traction suture is preferable.
- Superonasal or superotemporal quadrant is chosen. If the trabeculectomy fails , then the other quadrant is available for a second surgery.
- Antimetabolite (0.2 mg/ml Mitomycin C) is applied subconjunctivally for 2-3 minutes over a wide area and tailored according to the case and surgeon's preference. In high risk cases or failed trabeculectomy a higher dose (0.4 mg/ml) can be used.
- Partial-thickness (1/3-1/2 scleral thickness) scleral flap is made in either rectangular, triangular or square-shaped (base should be at least 4-5 mm wide) with a crescent knife or Bard-Parker blade according to the surgeon's preference.

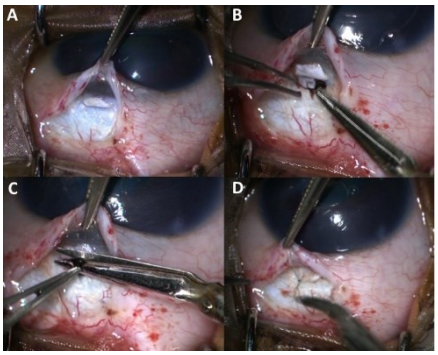


Figure: 1

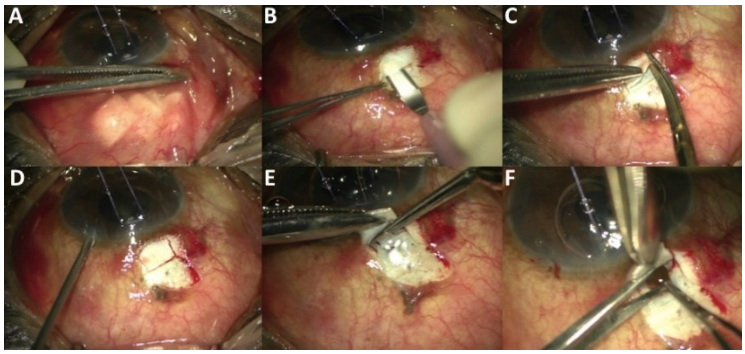


Figure: 2

Figure: 1 A-D: Intraoperative image showing steps of limbal based trabeculectomy. (A- scleral flap, B- sclerostomy, C- peripheral iridectomy, D- scleral falp suture)

Figure 2 A-F: Intraoperative image showing steps of fornix based trabeculectomy. (A: MMC application, B-D: scleral flap, E- sclerostomy, F- peripheral iridectomy)

- Anterior chamber paracentesis is done, and an air bubble is injected. The ideal scleral flap should extend till the clear cornea and air bubble should be visualized through the bed. Entry into the air bubble while making the ostium ensures that no other intraocular structures are injured. An AC maintainer can be used during surgery especially in eyes with high risk of choroidal effusion such as Sturge Weber Syndrome.
- Sclerostomy is made with an MVR blade and Vannas scissors or Kelley's punch, and a broad peripheral iridectomy is done. Any traction should be relieved at this time.
- The scleral flap is closed with fixed sutures and/ or releasable sutures . Again no traction to be given at this time to ensure proper closure and titrate flow .
- *Conjunctival closure:* In limbal-based surgery, continuous or interrupted sutures are used. In fornix-based surgery, two peripheral wing sutures and two mattress sutures are used. Inadequate suturing may lead to bleb leak in the early post-operative period.

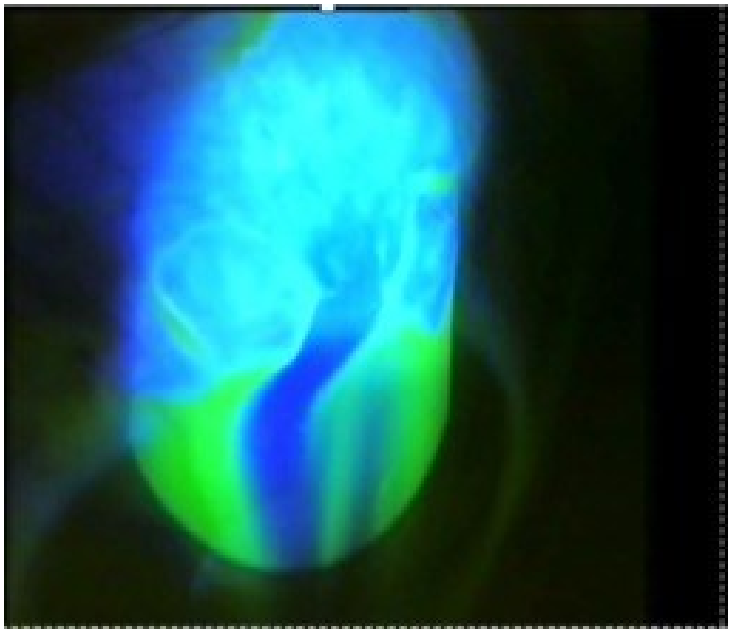


Figure: 3 (Seidel's test showing leak in post-operative period)

- Fluid can be injected from the side port and trypan blue dye spread over conjunctiva to check for any area of leakage and ensure water tight closure.
- Subconjunctival antibiotic-steroid combination to be given away from area of the bleb as it can lead to subconjunctival hemorrhage.

Why is it still the gold standard?

Trabeculectomy, since its first description in 1968, has stood the test of time and is still considered the gold standard surgical procedure for primary glaucomas. [1,7,8] Over a period of 20 years, trabeculectomy (without antifibrotics) has been shown to have an absolute success (IOP <21 mmHg, without any additional medication) rate of approximately 60% and qualified success (IOP <21 mmHg, with additional glaucoma medications) rate of approx. 90%.[9]

Some surgeons have started advocating glaucoma drainage devices as the primary surgical modality for glaucoma . This is not an appropriate strategy as whenever we do glaucoma surgery we must anticipate and plan for a future surgery if the first surgery fails. We may put a tube after the Trabeculectomy fails or do a revision trabeculectomy but putting in a second tube after the first has failed carries an increased risk of complications. In a comparative cost analysis, trabeculectomy was found to be most cost-effective when compared to a Baerveldt implant or medical therapy alone; in terms of cost per Quality-adjusted-life-year gained.[10] In addition there is a high risk of corneal endothelial damage when tubes are inserted in phakic eyes. In primary tube versus trabeculectomy study, at the end of 3 years, trabeculectomy with mitomycin C achieved lower IOP with use of fewer glaucoma medications when compared to tube shunt surgery.[11]

With their limited effectiveness, minimally invasive glaucoma surgeries fail to justify the cost of treatment in countries with limited healthcare resources and infrastructure. A conventional trabeculectomy, in the hands of a skilled and experienced surgeon, is the current gold standard and cost-effective surgical treatment for most cases of glaucoma. Trabeculectomy should be done when medical therapy is inadequate to reach target IOP, if glaucoma is progressing (visual field/Optic disc cup) and if patient is not compliant or not affording or has drug allergy.[12]

Where does it need improvement?

Trabeculectomy is prone to short and long term complications related to the surgical technique and especially the use of antifibrotic agents (Mitomycin C) . In the past few years many efforts have been made to prevent these surgical complications– the use of releasable sutures,[13–15] laser suturolysis to modulate the filtration;[16] the use of lower dosage of anti-metabolites over a large surface area;[17,18] the transition from a limbus-based to a fornix-based conjunctival flap;[19] and advent of the "safe surgery system"[20].

Interventions to improve the safety and efficacy of Trabeculectomy

Pre-operative measures-

Steroids: The use of multiple topical glaucoma medications causes conjunctival inflammation. This inflamed conjunctiva can affect the surgical success rate. It has been shown that pre-operative use of topical steroids (1% Fluorometholone four times daily) for 1 month can reverse the conjunctival changes caused by topical glaucoma medication and may help in improving the success rate of trabeculectomy.[21]

Anti-coagulants: Anti-platelet drugs like Aspirin, are known to pose an increased risk of hyphaema after trabeculectomy, but it does not appear to affect the surgical outcome. So, it appears safe to continue Aspirin during trabeculectomy. Patients on Warfarin are at risk of serious bleeding complications, and are at risk of trabeculectomy failure.[22]

Adnexal factors: Patients with blepharitis have a higher concentration of bacteria in and around the eye, leading to higher chances of infection after the surgery. Therefore, it is recommended to treat blepharitis before glaucoma surgery.

Intra-operative measures-

Subtenon's anaesthesia:

In case of using subtenon's anaesthesia, avoid injection in the bleb area, because any hemorrhage at this stage can increase the chances of failure.

Superior rectus traction suture:

Injuring the superior rectus muscle sheath can cause fibroblast proliferation into the trabeculectomy site. It has been found to be one of the risk factors for failure of trabeculectomy.[23]

Fornix based trabeculectomy:

It produces a diffuse mildly elevated bleb (ideal bleb). Although there is controversy as to which procedure is superior, compared to the limbal-based procedure.

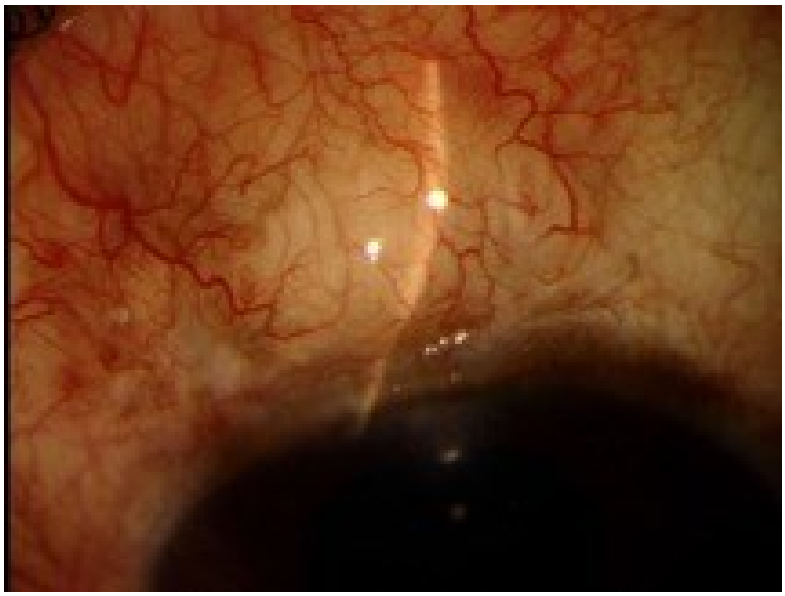


Figure: 4 Slit-lamp clinical picture of diffuse mildly elevated bleb following fornix based trabeculectomy

Anti-metabolites to modify wound healing:

Mitomycin-C is an anti-tumour antibiotic derived from Streptomyces caespitosus. It alters the conjunctival vascular endothelium and inhibits the proliferation of fibroblasts. These effects are prolonged and have been proven by numerous studies, to be beneficial for IOP control in primary as well as high-risk trabeculectomies. This drug, despite its benefits, can lead to short-term and long-term post-operative complications including thin-walled atrophic blebs, late bleb leaks, choroidal detachment, hypotony with or without maculopathy, cataract progression, blebitis and, endophthalmitis.[17,26,27] Hypotony has been reported in as high as 42.2% after a mean follow-up of 26.1 months, with almost 9% of the eyes developing hypotony maculopathy.[17]Numerous studies have been conducted over the years to determine the optimum dose, duration and site of MMC application to minimize the post-operative complications and maximize the life of the functioning trabeculectomy.[17,26,28–30] There is still no universally accepted protocol for the use of MMC in terms of concentration and duration of application. The Safe Surgery System (SSS) recommends using MMC based on estimated risk of failure, between 0.2 and 0.4 mg/ml for 3-5 min, applied to a large posterior area of bared sclera with soaked sponges, while keeping the edge of the conjunctiva free of the antimetabolite.[20]

Another anti-metabolite that has been used widely in trabeculectomy is 5-Flourouracil. The most commonly used concentration is 50 mg/ml for 3-5 minutes with a technique similar to that of MMC application. There is some evidence for relatively less epitheliopathy and less hyphema with MMC use.[18]

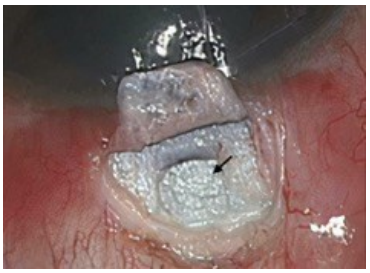
Measures to decrease MMC related complications:

Lowering the dosage and exposure time of intra-operative use of MMC can help reduce the significant sight threatening complications . [31,32] In a randomized control trial evaluating the efficacy of different doses of MMC in primary glaucoma, Sihota et al concluded that a 1-min subconjunctival application of 0.1 mg/ml MMC is non-inferior to 0.2 mg/ml and thinning of the bleb is significantly less frequent in the long term.[33] MMC dose can be increased in eyes with risk factors like failed trabeculectomy, secondary glaucoma or previous surgery involving conjunctiva.[34]

Role of Releasable:

Excessive filtration in the early postoperative period can lead to complications like hypotony, shallow anterior chamber, choroidal detachment. The use of releasable sutures (first described by Shaffer et al[35]) allowed the surgeons to make a relatively tight scleral flap closure intra-operatively, thus preventing early post-operative complications occurring due to excessive filtration.[36,37] The suture is ideally removed at the 2nd or 3rd week. It can be removed earlier if IOP is high even after massage/ medications, and at a later stage if an antimetabolite has been used. Releasable sutures are usually needed in patients with primary angle-closure glaucoma, neovascular glaucoma, and Sturge-Weber syndrome with glaucoma, aniridia with glaucoma but can be adopted in all patients for added safety.

Limited Deep sclerectomy combined with trabeculectomy and MMC: Making a deep scleral pocket creates an intrascleral lake which can increase success rate by preventing fibrosis.[34,38]



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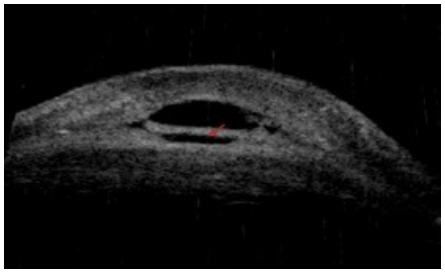

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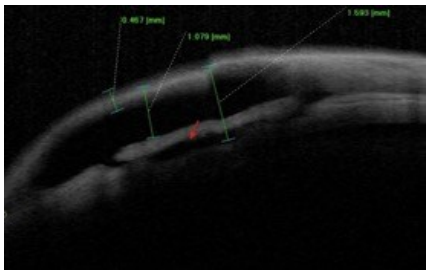


Figure: 7

Figure 5: Intraoperative image showing deep sclerectomy (black arrow)
Figure 6: UBM showing intrascleral lake (red arrow) after deep sclerectomy
Figure 7: ASOCT showing intrascleral lake (red arrow) after deep sclerectomy

An additional scleral dissection is done to 90% depth and short of the blue limbal transition zone to create a scleral reservoir and this also allows additional flow through the suprachoroidal space.

Role of Adjuvants

- There is *no benefit of adding anti-VEGF* to trabeculectomy except in patients with NVG neovascular glaucoma as there is no effect on safety or efficacy but a steep increase in surgical costs.[39]
- The use of biodegradable collagen implants in trabeculectomy as a replacement to MMC showed a lower success rate and its use as an adjuvant to trabeculectomy with MMC showed no added benefits.[40–44] We currently do not recommend the use of these implants for trabeculectomy as use of a low dose mitomycin C over a diffuse area is a better and lower cost option.

Post-operative measures:

Topical steroids: They should be given along with topical antibiotics at least for a period of 8-12 weeks in a tapering regimen. If there are signs of increased bleb vascularity, the steroids dosage and frequency can be augmented. Cycloplegia can be given for 1-2 weeks post surgery. The patient should be encouraged to have an early ambulation and adequate hydration. Plastic shield can be used at night to prevent inadvertent eye injury especially in children.

Role of oral steroids: There is no additional benefit of giving oral steroids routinely along with topical steroids after trabeculectomy.[45] It can be given peri-operatively in patients with uveitic glaucoma.

Role of Oral Doxycycline : In eyes with a small and early wound leak, conservative therapy with pad-bandage and oral doxycycline 100mg twice a day for two weeks can be given to promote fibrosis and plug the leak.[46]

Bleb needling can be performed in eyes with encysted bleb or failing blebs with increased vascularity. Bleb needling with antimetabolites has shown to have a complete success rate of about 60% at 2 years in failed trabeculectomy of eyes with primary glaucoma.[47,48]

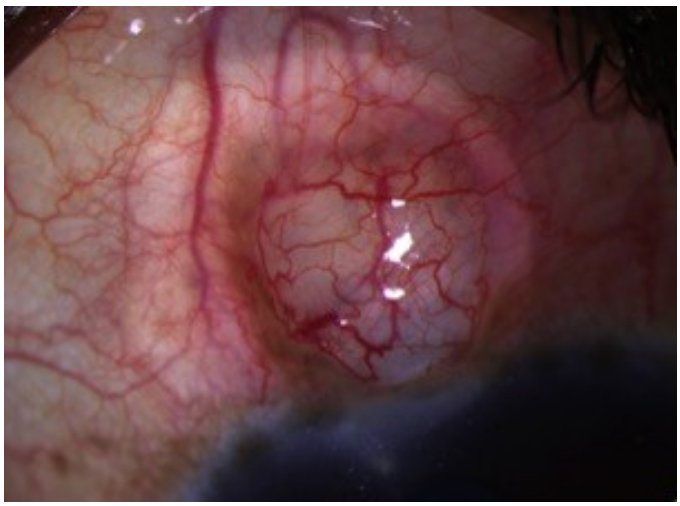


Figure: 8 Slit-lamp clinical picture showing localized, encapsulated bleb

Bleb needling can be done with injection of 5mg of 5-Fluorouracil taking care that it should not come in contact with the cornea due to its toxicity.[49] Injection of a cohesive viscoelastic bolus at the injection site followed by the 5FU injection prevents inadvertent leak from the injection site.

Bleb needling is not effective once the trabeculectomy has failed and there is dense fibrosis. In such situations a revision trabeculectomy at the same site or a second trabeculectomy at a different site can be performed.

Thin cystic bleb - This is a long term complication of trabeculectomy surgery. Surgical repair is needed in case of late bleb leaks , blebitis/endophthalmitis or hypotonic maculopathy at any stage of follow up

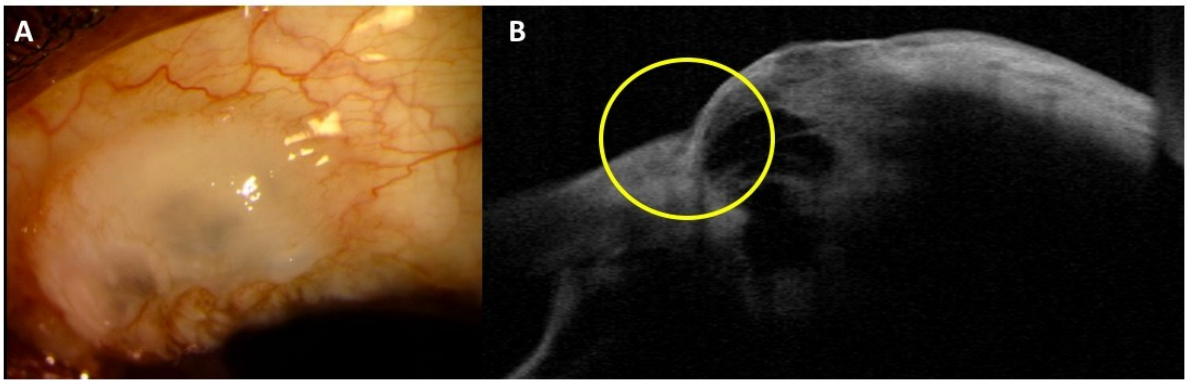
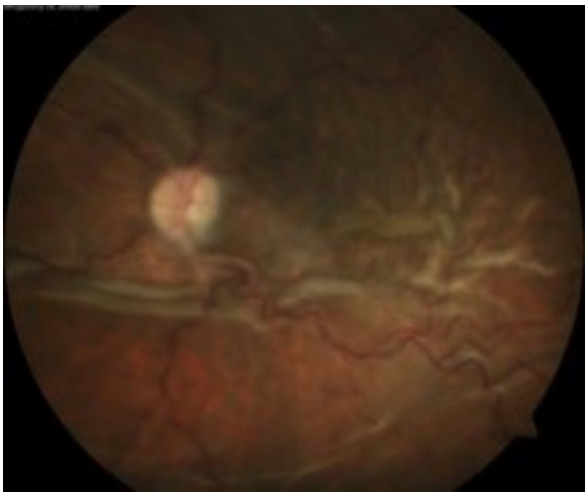


Figure: 9 A- Slit-lamp clinical picture showing thin cyctic avascular bleb, B- ASOCT of the bleb showing thin walled area (yellow circle)



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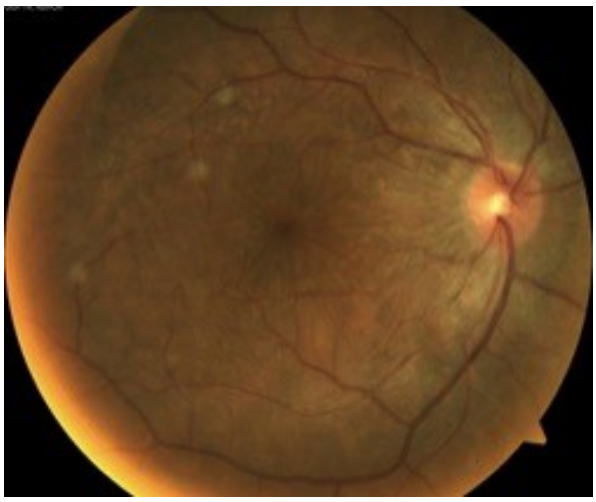

Figure: 11

Figure 10: Fundus clinical picture showing hypotony with choroidal detachment
Figure 11: Fundus clinical picture showing hypotonic maculopathy

The technique used is a simple conjunctival advancement after removing the dysfunctional bleb epithelium. In case of inadequate conjunctival availability- a conjunctival rotational pedicle flap or a conjunctival autograft from fellow eye (if blind) or inferior fornix can be done. In eyes with scleral necrosis/defect a Maumenees repair or scleral patch can be done.[50–52]

Long term surveillance - Blebitis and endophthalmitis is one of the dreaded long-term complications of trabeculectomy. All Trabeculectomy patients are at risk and should be explained about the symptoms (RSVP- redness, sensitivity to light, vision drop, pain) of infection and to be asked to use topical antibiotics (moxifloxacin) at the onset of symptoms and report to the nearby clinic/hospital as soon as possible for appropriate therapy. Its management depends upon the severity and includes topical fortified antibiotics, intravitreal or subconjunctival antibiotics, systemic antibiotics (oral or intravenous), and pars plana vitrectomy.

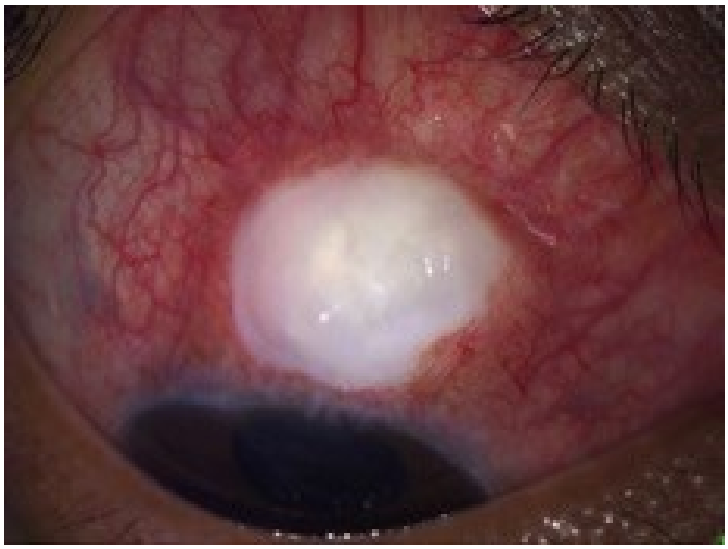

Figure: 12 Slit-lamp clinical picture showing blebitis with cyctic avascular bleb

In conclusion Trabeculectomy offers the best long term solution for IOP control in glaucoma patients. An appropriate management protocol with proper preoperative preparation, meticulous surgical technique with low dose MMC and releasable sutures and appropriate post-operative therapy with early recognition and treatment of complications is necessary to maintain its stature as the "Gold Standard".

Table 1:

Measures to improve trabeculectomy outcomes	
1	Pre-operative: • Explain to the patient about the surgery and its risk to vision, the importance of regular follow up, compliance with post-operative medications and need for repeat surgery • Check mobility of conjunctiva and any scarred area • Treatment of blepharitis/ meibomitis/dacryocystitis • Use of topical steroids to reduce conjunctival inflammation • Stopping oral anticoagulants prior to surgery
2	Intra-operative: • Avoid superior rectus traction suture • Use of fornix based conjunctival flap • Graded and judicious use of low dose MMC over a wide area • AC maintainer in high risk situations • Use of releasable sutures to prevent post operative shallow AC • No role of anti-VEGF or Ologen
3	Post-operative: • Adequate dose and duration of topical steroids • Timely removal of releasable sutures • Needling for encapsulated bleb/early bleb failure • Early recognition and treatment of bleb leaks (Oral Doxycycline)
4	Follow-up: • Explain to the patient about RSVP symptoms • Surgical bleb revision with conjunctival advancement in case of late bleb leak or cystic avascular bleb prone to infection or hypotony or bleb related endophthalmitis

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Notes:

WHAT IS NEW IN THE SURGICAL MANAGEMENT OF GLAUCOMA

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- **THE RESURGENCE OF ANGLE SURGERY**
- **NEWER GLAUCOMA DRAINAGE DEVICES ON THE HORIZON**

The first author wishes to acknowledge his mentor **Dr. Craig Chaya MD, Moran Eye Center** for having taught him GATT and BANG.

THE RESURGENCE OF ANGLE SURGERY

Introduction:

Trabeculectomy has been the gold standard in the surgical management of Glaucoma. While trabeculectomy reduces the intraocular pressures effectively, it is associated with a number of complications like failure, bleb leaks, infections, hypotony to name a few. The other alternative to surgical management is the implantation of a glaucoma drainage device. This again runs the risk of implant/tube exposure, corneal and anterior segment complications, failures, motility restriction etc.[1,2,3]

Given the limitations of current techniques, there has been a considerable interest in reviving the natural aqueous outflow pathways. This review shall focus on the resurgence in angle surgeries in recent years. We shall be describing the following surgeries in detail

Angle surgeries:

a) Gonioscopy assisted transluminal trabeculectomy
b) 360 degree trabeculotomy
c) Trabectome
d) Kahook Dual Blade (KDB)

Miscellaneous Procedures:

e) Presser Flo
f) Paul Glaucoma Implant

a) Gonioscopy Assisted Transluminal Trabeculectomy (GATT)

Trabeculotomy cleaves the trabecular meshwork and inner wall of Schlemm's canal offering a direct conduit of aqueous humor to the collector channels. It is estimated that these structures together constitute 75% of resistance to aqueous outflow with the collector channels accounting for the rest.[4,5] Trabeculotomy has traditionally been used in congenital glaucoma. The traditional "Harm's trabeculotomy" yields suboptimal results in adults. Cleaving the entire length of the trabecular meshwork and inner wall of the Schlemm's canal has greater efficacy. This was traditionally done through an "ab externo" approach after incising the conjunctiva and making a scleral flap. Grover et al

introduced a technique of incising and cannulating the Schlemm's canal through an "ab interno" approach – Gonioscopy assisted transluminal trabeculotomy (GATT) avoiding the need for conjunctival incisions. This preserves the conjunctiva for future "traditional" glaucoma surgeries, should GATT fail.[5,6,7]

Description of technique:

Preoperative evaluation and patient selection:

A detailed preoperative evaluation should include clinical history, applanation tonometry, gonioscopy, comprehensive anterior and posterior segment evaluation. Careful gonioscopy should be done to evaluate the entire extent of the angle. GATT is possible only if the angle is fully open with identifiable landmarks. Presence of aberrant/new vessels, goniosynechia/peripheral anterior synechiae are contraindications to the procedure. The glaucoma is staged based on the result of the visual fields, clinical exam and optical coherence tomography. The procedure involves a lot of manipulation in the anterior chamber. Therefore patients with a compromised corneal endothelium and lens subluxation/unstable posterior chamber intraocular lens are not suitable candidates either. Bleeding after surgery is universal and therefore patients who are on blood thinners should not be treated with these procedures. [5,7] It is preferable not to treat these patients with oral hypotensive agents on the day of surgery (Unlike in trabeculectomy). It has been our experience that having a turgid anterior chamber aids the procedure. Softening the globe before surgery results in blood reflux into the Schlemm's canal and uncontrollable bleeding on incising the trabecular meshwork. The procedure requires patient cooperation and it is best not to attempt the procedure in uncooperative patients. It can be done in phakic and pseudophakic patients and can also be combined with phacoemulsification and IOL implantation.

Technique (Video 1 & 2):

Video 1: Surgical Video showing author's technique of GATT
Link: https://youtu.be/aBfqlUz9Xml

Video 2: Surgical Video showing the technique of goniotomy, when the suture encounters an obstruction
Link: https://youtu.be/UtbU-1El8k4

The procedure is done under the operating microscope with surgical asepsis and topical anesthesia. The surgeon sits on the temporal side. The patient's head is tilted towards the opposite side, the patient is asked to look away from the surgeon and the microscope is tilted towards the surgeon. This enables an angle of around 60 degrees between the surgeon's view and the patient's gaze. Two side ports are made – one to the left of the surgeon approximately 3 clock hours away (11-12 O'Clock for the right eye and 12-1 O'Clock for the left eye) and the second to the right of the surgeon 1 clock hour away (7-8 O'Clock for the right eye and 4-5 O' Clock for the left eye) with a microvitreoretinal blade (MVR).

The anterior chamber is filled with ophthalmic viscosurgical device (OVD). We prefer to do phacoemulsification with IOL implantation prior to GATT (when indicated) through a temporal clear corneal incision this enables a better view of the angle. OVD is placed over the cornea and a direct gonio lens (Hill or other) used to view the angle. The trabecular meshwork is identified and MVR blade is used to incise the trabecular meshwork for around one clock hour and depress the posterior lip of the incised trabecular meshwork. A 5-0 or 6-0 Prolene® of sufficient length is blunted with gentle cautery to achieve a rounded tip. A lighted microcather (Ellex®) is ideal as the surgeon can monitor the progress in real time and identify misdirection into a collector channel or posteriorly. However this is an expensive proposition for developing countries.

The direct goniolens is removed and the blunted tip of the Prolene® suture is introduced into the anterior chamber through the left side port till the blunted tip rests near the angle. A micro forceps is used to feed the tip of the Prolene® suture into the Schlemm's canal under gonioscopic control. The suture is slowly advanced through the Schlemm's canal by grasping it close to the incised trabecular meshwork. Bleeding is common during the procedure. When this happens, the surgeon removes the microforeceps and introduces the cannula of the OVD syringe close to the site of bleed while the surgical assistant injects OVD. This moves blood away from the surgical site and tamponades further bleeding. When this fails to achieve sufficient view, the blood is washed with the Irrigation aspiration Hand piece. Corneal striae that hamper visualization can be minimized by avoiding pressure over the cornea (with the goniolens), having a turgid anterior chamber and minimizing torque with the second instrument. The surgeon/assistant should be able to identify a failure to further advance the suture. It is preferable not to attempt and force the suture further as this may result in a misdirection and false passage.

Many authors have reported that 360 degree cannulation during GATT may not always be possible. Collapse of the trabecular meshwork due to fibrosis caused by age or previous surgery may be a possible etiology and may cause the suture to stop.[8] The surgeon may retrieve the distal end by a goniotomy (after positioning the patient and operating microscope appropriately). The blunted tip acts as an anchor and enables goniotomy to the extent cannulated irrespective of where the suture is pulled.

Grover et al has suggested reverse cannulation to achieve 360 degree goniotomy in the event of an obstruction. If complete cannulation is successful, the distal end and the proximal are pulled to complete the goniotomy. An anterior chamber wash is given with the irrigation aspiration handpiece to remove blood and debris. An air bubble is placed in the anterior chamber at the end of the procedure. A 25 % OVD fill is also done to tamponade any postoperative bleeding and side ports hydrated. Grover et al has suggested a dye marked white nylon suture to enable monitoring the progress of the suture as the suture tip can be seen with the operating microscope without the use of a gonioscope.[9] This suture is not available in India to the best of our knowledge. We use a Hill goniolens to view the suture tip by positioning the microscope and patient appropriately.

Postoperatively the patient is placed on a topical broad spectrum antibiotics four times a day for 1 week, loteprednol eight times a day tapered over six weeks, topical NSAID for six weeks and pilocarpine 2% four times a day for four weeks. Patients are reviewed on the first postoperative day, first postoperative week (most of the postoperative hyphemas happen during the first week), and sixth postoperative week. Gonioscopy is done at or after six weeks. A trabecular shelf

Figure: 1
Gonioscopy 6 weeks after GATT showing the trabecular shelf (arrow)

is seen in most patients at least to some extent of the distance cannulated. A note should be made of goniosynechiae if any.

Complications:

This procedure has a learning curve and it needs 20-30 instructed surgeries before the novice surgeon can do it alone. As in any angle based procedure, it is important to view the entire angle in a preoperative gonioscopy, so as to ensure that there are visible landmarks. It has been our experience that it may be difficult to cannulate the Schlemm's canal (at all or for sufficient length) in all patients. This is presumably due to a collapsed trabecular meshwork.[8] We usually abandon the procedure in these circumstances or do a BANG (described later). It is advisable not to attempt a trabeculectomy during the same sitting as no hypotensive agents have been given on the day of surgery. This could result in severe positive pressure during trabeculectomy. The procedure shares the complication of any intraocular procedure and the list of complications would include iris chafing, cyclodialysis, endophthalmitis, and cystoid macular edema to name a few. Complications specific to the procedure include

- Descemet's membrane detachment – caused by manipulation in the anterior chamber. May need repositioning and reattachment.[10]
- Hyphemas – We advise bed rest for a couple of days with head end elevation to minimize the incidence. If blood enters the capsular bag in pseudophakic patients resulting in intracapsular hematoma, it seldom clears on its own and may need surgical wash if it obscures the visual axis.[11]Severe bleeding into the anterior chamber or hyphema that fails to clear spontaneously may need a surgical wash

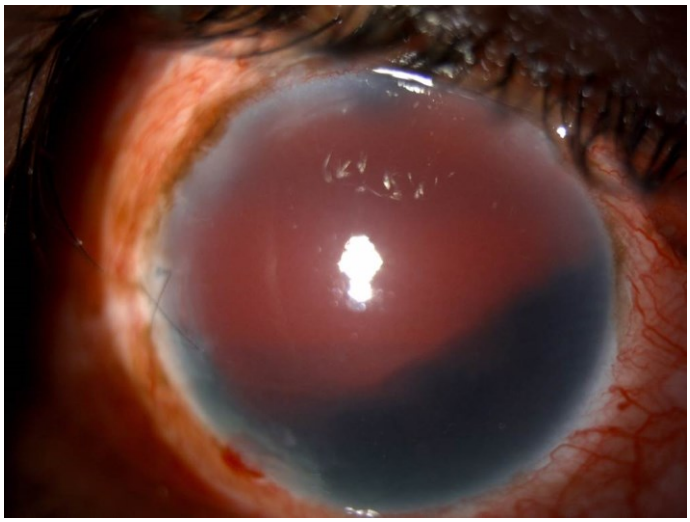

Figure: 2
Total hyphema 5 days after 360 degree GATT that needed a wash

- Goniosynechiae: Grover et al has recommended the use of Pilocarpine in patients at risk of this complication. We have seen goniosynechiae form in spite of pilocarpine use. The significance of this finding is not known, but it is logical to assume that the procedure will fail if extensive goniosynechiae form. [10]
- Failure: currently there is no technology to assess the patency and health of downstream collector channels that are crucial to the success of the procedure. An episcleral venous fluid wave during anterior chamber wash at the end of goniotomy is proof of patency of the collector channels and some studies have shown a correlation between success rates and the quadrants of episcleral venous fluid wave at the end of the procedure. The advantage of this procedure is that it leaves the conjunctiva untouched for any future procedures. [10]

What the published studies say[5,6,7,8,12]

- The reported success rates range from 60-97%
- The percentage IOP drop in IOP ranges from 10% to 42%
- Follow up data of a maximum of 2 years published
- Incidence of hyphema ranges from 1.4-68%.
- Only retrospective studies published. No randomized control trials

360 degrees ab interno TRABECULOTOMY:

The aim of angle surgeries is to rejuvenate the physiological outflow unlike trabeculectomy which creates a nonphysiological drainage site and is fraught with complications. This procedure does not need expensive investment or a power source. The device has a blue roller on the surface and a metal tip (figure on https://webeye.ophth.uiowa.edu/eyeforum/tutorials/migs/MIGS-5a-LRG.jpg & https://www.beye.com/product/trab360-trabeculotomy-system, accessed on 7th March 2021). Under surgical asepsis, after appropriately positioning the patient, the anterior chamber is entered with a 2.2mm Keratome and filled with viscoelastic (after injecting intracameral preservative free lignocaine). The tip of the trab360 is used to pierce the trabecular meshwork and the roller used to advance the probe. Once the probe is advanced 180 degrees, the surgeon cleaves the trabecular meshwork using a push pull movement. The Schlemm's canal is now cannulated in the reverse direction and the process repeated. This procedure has similar complications as GATT. It is easy to mistake the anterior ciliary body for the trabecular meshwork and misdirect the probe thereby causing iris root or ciliary body damage. [13]

The Kahook Dual Blade: The Kahook Dual Blade is a disposable single use stainless steel blade that allows an excisional goniotomy of the trabecular meshwork. It has a ramp that enables lifting of the trabecular meshwork together with blades at the side. (https://www.beye.com/product/kahook-dual-blade%20accessed%20on%201st%20August%202021) At the end of the procedure, the incised trabecular meshwork is removed with the aid of a micro forceps. The blade is micro engineered to facilitate insertion into the anterior chamber through a MVR entry. 120 degrees of goniotomy with the KDB has been shown to have equivalent results to 360 degree GATT. The authors suggested that this could be because KDB provides for an excisional goniotomy (hence less likely to close) and GATT is an incisional goniotomy (the leaflets may fuse and close the cleft). The procedure is simple and has a minimal learning curve. [14,15] A cheaper alternative is the use of a bent 25/26G needle to engage and strip the trabecular meshwork termed the BANG (bent angle needle goniotomy)

Video 3: Surgical Video showing author's technique of BANG (bent angle needle goniotomy)
Link: https://youtu.be/uPbk3uBCEwg

We use this technique whenever there is a difficulty in cannulating the Schlemm's canal during GATT.

Trabectome (ab interno goniotomy): The trabectome consists of a console and a disposable handpiece. The hand piece has a pointed tip to allow penetration into the trabecular meshwork, a radiofrequency unit that cauterizes the trabecular meshwork and an aspiration port that aspirates the debris. There is an irrigation port that maintains the anterior chamber. Viscoelastic is typically not used as it may make the view hazy by trapping air bubbles released during ablation of the trabecular meshwork. The power is typically set at 0.8 mW and the recommended range is 1-3 mW. The advantage of this procedure is that patients with partially closed angles (so that there is some space to engage the instrument in the trabecular meshwork) can also be treated. The instrument is thus excellent for goniosynechiolysis. Movement of the instrument in the anterior chamber should be gentle as forceful movements risk iridodialysis and cyclodialysis. It can be done before/after cataract surgery. Trabectome ablation can also be done in phakic patients and there is no evidence that this hastens cataract progression.[16,17]

The Presser Flo implant (formerly called the Innfocus microshunt)

The Presser flo implant (video available at https://www.youtube.com/watch?v=lXPhAFrSNyk accessed on 2nd March 2021) is a new 8.5mm long valveless implant made of a novel polymer called SIBS. This material is stretchy, non-biodegradable and it is suited for long term implantation in the eye as it

provokes minimal inflammation and is expected to outlive the patient. It is thermoformable (unlike a silicone tube which slowly straightens over time necessitating a patch graft to prevent exposure) and molds to the shape of the eye. It is implanted by an ab-externo approach under local anaesthesia (peribulbar/subtenon's). After conjunctival incision, the area is treated with PVA sponges soaked in 0.2-0.4mg/ml mitomycin for 2-3 minutes applied close to the limbus. A thorough wash is given with 30ml of BSS and a scleral pocket is made starting 3mm away from the limbus. A 25 G needle is used to enter the anterior chamber. The implant is provided with wings that are tucked into the scleral pocket. These prevent hypotony and anchor the implant thereby preventing migration. When correctly implanted, the tube should bisect the angle and the distal end rests 6mm from the limbus thereby aiding a distal drainage. Flow is established by gently pressing on the globe or flushing the tube. The lumen of the tube (70µm) was designed based on the Hague Poiseuelle equations which suggests that this lumen is large enough to allow drainage (larger than the size of sloughed corneal endothelial cells -40-50µm) and small enough to prevent hypotony (the tube is not ligated). The conjunctiva and tenon's are closed over the tube taking care not to occlude the lumen. Advantages of the device include minimal scleral dissection, posterior drainage and low incidence of hypotony. There is limited experience of use of this device and there is need for data from long term trials with larger number of patients.[18,19]

NEWER GLAUCOMA DRAINAGE DEVICES ON THE HORIZON

The Paul Glaucoma implant

Baerveldt glaucoma implant (BGI) and Ahmed glaucoma valve (AGV) are the most commonly implanted glaucoma drainage devices. These devices have a internal tube diameter of 0.3mm and outer diameter of 0.64mm. When implanted in the anterior chamber angle they occupy close to 50% of the 0.75mm angle. the BGI has a larger surface area of 350mm^2 compared to the 184mm^2 of the AGV, which probably gives a better IOP reduction. Much of the BGI however is tucked under the rectus muscles and it is unclear if these areas are functional. The Paul Glaucoma Implant is a newly introduced silicone implant that attempts to circumvent some of these disadvantages. The device has a surface area of 342mm^2, slightly less than that of the BGI. It however has a larger anteroposterior length but a shorter wingspan, which may increase the functional area. The lumen diameter is smaller -0.127mm and the outer diameter is 0.467mm which facilitates a safer implantation in the anterior chamber angle and minimizes the incidence of hypotony. The use of a ligature/internal stent is optional.[20]

Summary and Conclusions

There is a rekindling of interest in minimally invasive angle based glaucoma surgeries for justifiable reasons. These techniques have a learning curve and it behoves the learning surgeon to appropriately select cases. The short term efficacy and safety of these techniques are well established. Many of them do not require expensive equipment and are therefore suited for developing countries. Long term randomized controlled clinical trials are needed to establish the efficacy of these techniques and compare them with trabeculectomy or glaucoma drainage devices.

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Notes:

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